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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The effects of white phosphorus-felt smoke as a potential teratogen in producing a dominant lethal mutation (DLM) or on reproduction in a single generation (SG) in rats were investigated. Pregnant rats were exposed to WP-felt smoke in concentrations of 0, 500, or 1,000 mg/m^3 for 15 min/day for 10 consecutive days. On day 20 of gestation, their fetuses were derived by Caesarean section. One control pup had unilateral anophthalmia and one had narrow atria. One from the 1,000 mg/m^3 group had a short tongue and one had narrow atria and a

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19. KEYWORDS (Contd)

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Viability index

20. ABSTRACT (Contd)

thin-walled heart. Proven (successfully mated) male rats for the DLM study were exposed to the same conditions 5 days/week for 10 weeks and were mated with two groups of virgin females for 1 week each. The first group of females mated to males exposed to the 500 mg/m^3 dose had significantly more dams with at least one resorption than did the group mated to control males.

Males in the SG study were exposed to the same conditions as the DLM males; the females were exposed to these conditions for the last 3 weeks of the males' exposures. Pups born to the dams in the 1,000 mg/m^3 group had significantly lower body weights on all weighing days. They also had significantly lower indices of viability and survival.

It is probable that, at the doses used in these studies, WP-felt cannot be considered a teratogen nor does it produce dominant lethal mutations. It might, however, cause lower birth weights and retard the rate of development in the rat.

PREFACE

The work described in this report was authorized under Project 1L162622A554, Smoke and Obscurants; Technical Area 4-E, Smoke Toxicology. This work was started in August 1978 and completed in June 1979. The experimental data are contained in notebooks 9833 and 9963. Pathological information is recorded in a pathology accession book and in a yearly protocol book and is placed on file in the Comparative Pathology and Surgery Branch, Veterinary Medicine Division, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010.

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as promulgated by the Committee on Revision of the Guide for Laboratory Animals' Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council.

Acknowledgments

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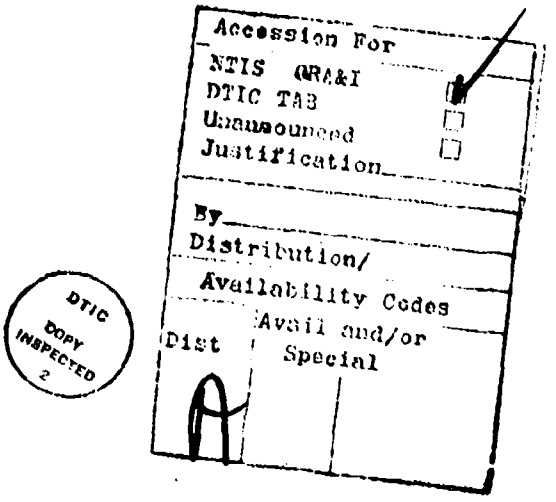

CONTENTS

WHITE PHOSPHORUS-FELT SMOKE: EFFECTS ON REPRODUCTION IN THE RAT

1. INTRODUCTION

The effectiveness of white and red phosphorus in generating smokescreens has been increased by the addition of butyl rubber plasticizers and felt. Unprotected troops in training exercises or combat are likely to inhale the smoke once a screen has been deployed. For this reason, it is imperative that the toxicity and health hazards of the smoke be known. Included in these categories would be the effect of smoke on mammalian reproductive and developmental processes; i.e., teratogenic potential.

Although there are data in the literature citing some of the signs of phosphorus poisoning,[1,2] there is no information available on the effects of white phosphorus (WP) smoke or white phosphorus-felt smoke on mammalian reproduction. To provide such data, personnel in this laboratory initiated studies to evaluate the potential for inhaled white phosphorus-felt smoke to produce teratogenic and dominant lethal mutation (DLM) effects and/or adversely affect reproduction in a single generation.

2. MATERIALS AND PROCEDURES

2.1 Materials.

2.1.1 Animals.

Sustained-barrier, pathogen-free, random-bred colony rats, AMRI:(SDxWI), were obtained from Veterinary Resources Branch, Veterinary Medicine Division, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010.

2.1.2 Housing.

The rats were housed in an air-conditioned building in a 1250 ft^2 room. The temperature was 70.75°F ± 5.37° and the humidity was 46.43% ± 14.44%. The lighting was manually controlled: 10 hours of light and 14 hours of dark. The housing cages, Model 18730, were made of 19 by 10.5 by 8.5-inch polycarbonate plastic. The cages were obtained from Laboratory Products, Inc., Garfield, New Jersey. The bedding that was used was San-i-cel, which was obtained from Paxton Processing Company, Inc., Laurel Farm, White House Station, New Jersey.

2.1.3 Food.

The food that was used was Wayne mouse and rat diet and it was obtained from Allied Mills, Inc., Chicago, Illinois. Tap water was contained in Nalgene polypropylene bottles which were obtained from J&E Berge, Inc., South Plainfield, New Jersey. Food and water were available *ad lib*.

2.1.4 Chemicals.

Smoke was generated from electrically ignited felt pellets impregnated with white phosphorus. Chamber concentrations were controlled by varying the size of the pellets and monitored by chemical analysis of bubbler samplers. The concentrations to which rats were exposed were 0, 500, and 1,000 mg/m^3.

2.1.5 Exposure Chamber.

A 20,000-liter cylindrical exposure chamber was used. The cages that were used for exposure were stainless steel, and they were compartmentalized to hold 10 rats each. The cages were placed on racks inside the chamber. The chamber temperature was 76°F ± 6.44°, and the relative humidity was 45% ± 29.2%.

2.2 Procedures.

The studies on reproduction reported here were conducted in a manner that insured coverage of specific events in the reproductive cycles of male and female rats that were considered essential to each study (i.e., spermatogenesis, oogenesis, copulation, organogenesis, gestation, birth, and postnatal care and development). In both the dominant lethal mutation and the single-generation studies, 13-week-old male rats were exposed to smoke or control air 15 minutes/day, 5 days/week, for 10 consecutive weeks prior to mating. This period incorporated a complete cycle of spermatogenesis. Females in the single-generation study were exposed for 3 weeks (15 minutes/day, 5 days/week), prior to mating to cover 4 to 5 estrus cycles.[3] Both the males and the females were exposed during their mating period. The females were exposed throughout their periods of gestation (21 days), and they and their neonates were exposed until the neonates reached the weaning age of 21 days (figure 1).

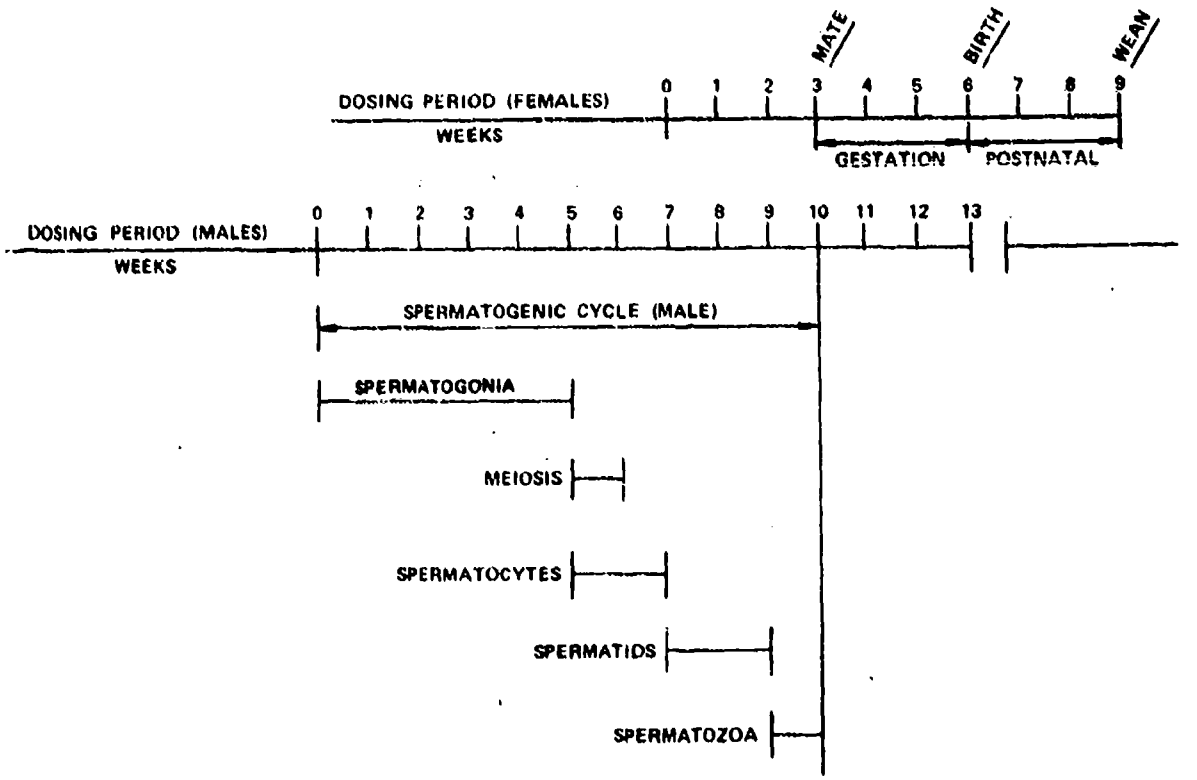

Figure 1. Exposure Chart for Dominant Lethal Mutation and Single-Generation Studies

In the teratology study, pregnant females were exposed for 15 minutes/day on 10 consecutive days beginning on day six of gestation. This is the period of organogenesis in the rat (figure 2) when the fetus is most sensitive to teratogens.[4]

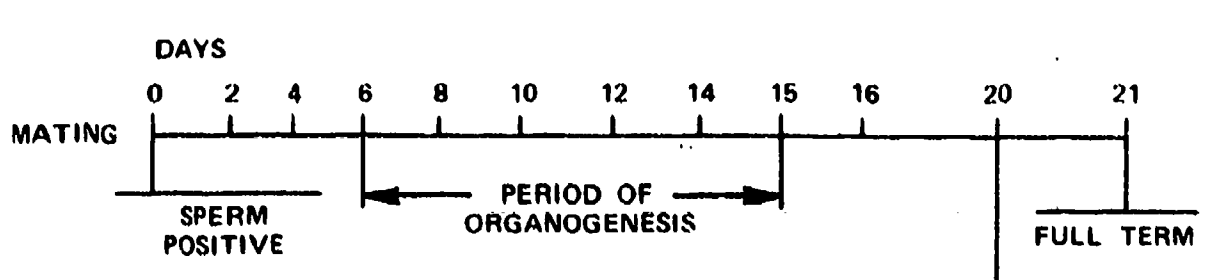

Figure 2. Chart of Events for Teratology Study in the Rat

2.2.1 Teratology Screen.

Each of 45 12-week-old males was mated to two 12-week-old virgin females. The exact day of insemination was determined by the presence of sperm in the vaginal washings of the females. The females were checked for sperm each morning. The day on which sperm was found in the washings was considered day zero of gestation.[5]

Females found to contain sperm in their washings were assigned, two at a time, to the control group or one of the two dose groups until there were 24 each in the control and low-dose group and 36 in the high-dose group. Male rats from these matings were then used as the proven males in the DLM study.

The exposure period for the inseminated females began on the calculated sixth day of pregnancy and continued 15 minutes per day, for 10 days, to the 15th day of pregnancy. On day 20 of gestation, 20 dams in each exposure group were sacrificed and the fetuses were delivered by Caesarean section. The data recorded were the total number of implantation sites in each uterine horn, the number of viable fetuses, and the number of resorptions. Upon removal from the uterus, each fetus was examined grossly for external abnormalities and then sexed and weighed. Half of each litter was placed in 95% ethanol and the other half of the litter was placed in Bouin's fixative and later examined for visceral abnormalities using the serial sectioning technique of Wilson.[4] Fetuses in ethanol were eviscerated at a later date and stained with alizarin red for evaluation of the skeletal system. This is a modification of the staining method by Hurley.[6] The experimental design appears in table 1.

Table 1. Experimental Design for Smoke WP-Felt Teratology Screen

Treatment	Number mated	Number pregnant	Exposure	Remarks
Control (air)	24	20	Days 6 to 15 of gestation	Twenty females were euthanatized on day 20 of gestation. Fetuses were fixed or stained and examined for visceral or skeletal abnormalities
500 mg/m^3	24	20	Days 6 to 15 of gestation	
1,000 mg/m^3	24	18	Days 6 to 15 of gestation	

2.2.2 Dominant Lethal Mutation Screen.

Twelve of the proven males from the teratology screen were randomly assigned to each of the study's three exposure levels. Each group was exposed for 10 weeks to the control atmosphere or the 500- or 1000-mg/m^3 WP-felt smoke for 15 minutes/day, 5 days/week. During the week following the exposure period, each male was housed for 5 days with two 12-week-old virgin females for mating. These females were then removed. During the second week after exposure, the males were housed for mating with a second pair of virgin females for 5 days and then separated. The females were euthanatized 11 days after their respective separation from the males. At that time, they were autopsied to ascertain pregnancy and to record numbers of viable fetuses, fetal deaths, and corpora lutea, which were analyzed using Student's "t" test, the Freeman-Tukey arc sine transformation followed by Student's "t" test, and chi square, respectively. The experimental design appears in table 2.

Table 2. Experimental Design for Dominant Lethal Mutation Screen

Group	Number of males exposed for 10 weeks	Number of exposed males used for mating	Number of unexposed females mated to exposed males, 1st week after exposure	Number of unexposed females mated to exposed males, 2d week after exposure
Air control	10	10	20[+]	20[+]
Low dose, 500 mg/m^3	18[++]	10	20[+]	20[+]
High dose, 1,000 mg/m^3	18[++]	10	20[+]	20[+]

[+]Females euthanatized on day 19 after initiation of mating and examined for fetal deaths and live implants.

[++]Due to exceptionally high number of expected deaths, additional males were used in both the 500 mg/m^3 and 1,000 mg/m^3 groups.

2.2.3 Single-Generation Study.

Groups of 12 12-week-old male rats were exposed to each exposure condition 15 minutes/day, 5 days/week, for 10 weeks to cover a complete spermatogenic cycle. Groups of 24 12-week-old virgin female rats were exposed similarly for 3 weeks to cover 4 to 5 estrogenic cycles, which were timed to coincide with the last 3 weeks of exposure of the males. The following week, the animals were caged for mating, two females per male. Exposure of the females was continued but exposure of the males was ended. Gravid females were exposed through their entire gestation period and continued to be exposed, after whelping, with their neonates. Exposure for each dam and litter ended when the neonates were 21 days old. During this period, each pup was re-examined and weighed 24 hours, 4, 7, 14, and 21 days after birth. After weighing on day 21, two pups of each sex from each litter were euthanatized and examined for gross external and visceral abnormalities. If no abnormalities were found in these, the remaining pups were assumed to be normal and were euthanatized and discarded. If abnormalities were found among the first four, then each remaining pup in the litter was euthanatized and examined to determine the frequency of the abnormalities within the litter. The data from this study were analyzed using Student's "t" test. The experimental design appears in table 3.

Table 3. Single-Generation Reproduction Study Experimental Design

Group	Number of males exposed 10 weeks prior to mating	Number of females exposed 3 weeks prior to mating	Number of females mated to each male	Weighing days for pups after parturition	Number of autopsied pups from each litter for gross external and visceral examination
Air control	12	20	2	1, 4, 7, 14, and 21	4 (2 males, 2 females)
Smoke, WP-felt, 500 mg/m^3	12	20	2	1, 4, 7, 14, and 21	4 (2 males, 2 females)
Smoke, WP-felt, 1,000 mg/m^3	20[†]	32[†]	3[†]	1, 4, 7, 14, and 21	4 (2 males, 2 females)

[†]Due to an exceptionally high number of anticipated deaths (reference 2), additional males and females were used in the 1,000 mg/m^3 group.

3. RESULTS

3.1. Teratology.

Twenty dams were randomly selected from among the 24 in the air control and 500 mg/m^3 dose groups. These, along with the 18 surviving dams in the 1,000 mg/m^3 dose group, were euthanatized using CO_2. The fetuses were Caesarean derived, counted, sexed, and weighed. The pregnancy data for the dams, the number and condition of the implants, and fetal weight appear in table 4. There were three major external abnormalities found among the fetuses: unilateral anophthalmia in one control fetus, a short tongue in one low-dose fetus, and brachygnathia in one high-dose fetus.

Table 4. Teratologic Effects on Pups of Female Rats Euthanatized on Day 20 after Inhalation of Smoke, WP-Felt, During Organogenesis

Condition	Dose level		
	Air control	500 mg/m^3	1,000 mg/m^3
Number of pregnant females	20	20	18
Percent pregnant	100	100	90
Total implants	238	242	221
Live implants	225	236	206
Dead implants	13	6	15
Percent dead implants	5.46	2.43	6.79
Mean weight in grams			
Male	3.91 ± 0.32	3.83 ± 0.36	3.87 ± 0.38
Female	3.76 ± 0.34	3.67 ± 0.30	3.66 ± 0.40
Mean body weight of all pups	3.84 ± 0.33	3.76 ± 0.34	3.77 ± 0.40
Average implants per pregnant female	11.90 ± 1.45	12.10 ± 1.37	12.28 ± 1.96
Average live implants per pregnant female	11.25 ± 1.41	11.80 ± 1.61	11.44 ± 2.28
Average dead implants per pregnant female	0.65 ± 0.67	0.30 ± 0.57	0.83 ± 1.10

Upon examining the fetuses fixed in Bouin's solution for visceral abnormalities, it was determined that nine of the fetuses in the high-dose group had right ductus arteriosus. One fetus in the high-dose group exhibited brachygnathia, five had prominent renal pelvises, and one had narrow atria and a thin-walled heart. Three fetuses in the high-dose group had ectopic testicles. One fetus in the low-dose group had signs of hemorrhaging around the eyes and one had a short tongue. Three had prominent renal pelvises, one had narrow atria, four had ectopic kidneys, and one had underdeveloped testicles. One fetus in the control group exhibited unilateral anophthalmia. Four had prominent renal pelvises, three had underdeveloped testicles, one had narrow atria, and one had an ectopic kidney. The brachygnathia, narrow atria, thin-walled hearts, and short tongue were the major abnormalities seen in the treated groups and, aside from the hemorrhaged eyes and increased incidence of ectopic kidneys in the low-dose group, there were no minor variations of significantly higher frequency in the treated groups than in the control groups. The data are shown in table 5.

Examination of the skeletal systems of the fetuses prepared for this portion of the study revealed no major abnormalities. There were several minor skeletal variations. Three types (14th rib, hypoplasia of the sternebrae, and dumbbell-shaped vertebra) were most frequent in the low-dose group and two other types (dumbbell-shaped sternebrae and cleft sternebrae) were highest, or equally as high, in the control group. Only for the sixth type, hypoplasia of the xyphoid process, was the frequency of the variation highest in the high-dose group. These data are summarized in table 6.

3.2 Dominant Lethal Mutation.

The males used in this study had successfully impregnated females in the teratology study. They were, therefore, proven males and each male again successfully impregnated at least one of the females made available in each of the two mating periods (table 7).

Table 5. WP-Felt Smoke Visceral Variations and Abnormalities

Visceral variations and abnormalities	Air control	Low dose, 500 mg/m^3	High dose, 1,000 mg/m^3
Prominent renal pelvis	4	3	5
Ectopic kidney(s)	1	4	
Narrow atrium	1	1	1
Thin-walled heart			1
Reversed ductus arteriosus			9
Underdeveloped testicles	3	1	
Ectopic testicles			3
Hemorrhagic eyes		1	
Anophthalmia, unilateral[+]	1		
Short tongue[+]		1	
Brachygnathia[+]			1

[+]Abnormalities.

Table 6. WP-Felt Smoke Skeletal Variations

Skeletal variations	Air control	Low dose, 500 mg/m^3	High dose, 1,000 mg/m^3
Fourteenth rib extra (rudimentary)	16	39	25
Cleft sternebrae	2	0	2
Dumbbell-shaped sternebrae	16	7	6
General hypoplasia of the sternebrae	35	46	38
Dumbbell-shaped vertebra - thoracic	9	11	2
Hypoplasia of xyphoid process	2	11	19

Table 7. WP-Felt Dominant Lethal Mutation - Male Fertility

Controls			500 mg/m^3 dose			1,000 mg/m^3 dose		
Male number	Females pregnant		Male number	Females pregnant		Male number	Females pregnant	
	Week 1	Week 2		Week 1	Week 2		Week 1	Week 2
1	1	2	1	2	2	1	2	3
2	1	2	2	2	2	2	2	3
3	2	2	3	2	2	6*	2	3
4	1	1	4	2	2	7	2	2
5	2	2	5	2	2	8	1	2
6	1	2	6	1	2	10	3	2
7	1	2	7	2	2	11	3	1
8	2	2	8	2	2	12	3	2
9	2	2	9	2	2			
10	1	2	10	2	2			

*Animals 3, 4, 5, and 9 died from the exposure to smoke.

On the estimated 18th day of gestation (assuming conception occurred during the first 24 hours of cohabitation), each female was euthanatized using carbon dioxide. Examination of their uterine horns showed that, for the first mating, significantly more females mated to males which had been exposed to 500 mg/m^3 had one or more resorptions (early deaths) than did females mated to control males. There were no significant differences found in any of the other parameters measured for any of the other groups, including the second mating females for the 500 mg/m^3 group. All parameters and indices appear in table 8.

3.3 Single Generation.

In this study, each male, except one in the control group and one in the 500-mg/m^3 dose group, impregnated at least one of the females available for mating. Of the females delivering, none had pups which showed any abnormalities. There were no significant differences among the three groups in the number of pups per litter. The body weights of the pups in the 1,000-mg/m^3 dose group were significantly lighter than those of the control pups on the first and each subsequent weighing day as determined by using Student's "t" test at $p = 0.05$ (table 9).

The survivability, viability, and lactation indices of the 1,000-mg/m^3 dose group were significantly lower than those of the 500-mg/m^3 and control groups (table 10). The dams and pups in the 1,000-mg/m^3 group were weakened by each exposure. Nursing often did not resume for 2 to 3 hours after exposure.

Table 8. Reproductive Data for Female Rats Mated to Males Exposed to WP-Felt Smoke

Numbers in parentheses indicate the number in each category.

Group	Week	Number mated	Number pregnant	M.I.	C.L.I.	I.I.	P.I.L.I.	F.I.	R.I.	N.V.F/V.F.	N.V.F. ≥1		N.V.F. ≥2	
Air control	1	20	14	70	(183) 13.07	(165) 11.79	(18) 1.29	(158) 11.29	(7) 0.50	7/158 = 0.04	5/9	36%	2/12	14%
	2	20	19	95	(253) 13.32	(238) 12.53	(15) 0.79	(223) 11.74	(15) 0.79	15/223 = 0.07	9/10	47%	4/15	21%
500 mg. m^3	1	20	19	95	(257) 13.53	(224) 11.79	(33) 1.74	(210) 11.05	(14) 0.74	14/210 = 0.07	13/ 6*	68%	1/18	5%
	2	20	20	100	(278) 13.90	(259) 12.95	(19) 0.95	(249) 12.45	(10) 0.50	10/249 = 0.04	7/13	35%	3/17	15%
1,000 mg. m^3	1	20	18	90	(256) 14.22	(226) 12.56	(30) 1.67	(215) 11.94	(11) 0.61	11/215 = 0.05	8/10	44%	2/16	11%
	2	20	18	90	(255) 14.17	(219) 12.17	(36) 2.00	(215) 11.94	(4) 0.22	4/215 = 0.02	4/14	22%	0/18	0%

NOTE: Abbreviations used:

$$\text{M.I. (mating index)} = \frac{\text{total number of females pregnant}}{\text{total number of females mated}} \times 100$$

$$\text{C.L.I. (corpora lutea index)} = \frac{\text{total number of corpora lutea}}{\text{total number of pregnant females}}$$

$$\text{I.I. (implantation index)} = \frac{\text{total number of implantation sites}}{\text{total number of pregnant females}}$$

$$\text{P.I.L.I. (pre-implantation loss index)} = \frac{\text{total number of corpora lutea-total number of implantation sites}}{\text{total number of pregnant females}}$$

$$\text{F.I. (fetal index)} = \frac{\text{total number of viable fetuses}}{\text{total number of pregnant females}}$$

$$\text{R.I. (resorption index)} = \frac{\text{total number of (early plus late) deaths}}{\text{total number of pregnant females}}$$

$$\text{N.V.F./V.F.} = \frac{\text{total number of nonviable fetuses}}{\text{total number of viable fetuses}}$$

$$\text{N.V.F.} \geq 1 = \frac{\text{total number of females with one or more nonviable fetuses}}{\text{total number of females with zero nonviable fetuses}}$$

$$\text{N.V.F.} \geq 2 = \frac{\text{total number of females with two or more nonviable fetuses}}{\text{total number of females with one or zero nonviable fetuses}}$$

* Significant at $p = 0.05$.

Table 9. Reproductive Data on Dams and Litters Exposed to WP-Felt Smoke

Group	Days	Number of males	Mean wt and SD*	Number of dams	Average litter size	Postnatal loss	Number of females	Mean wt and SD*	Average litter size	Postnatal loss
						%				%
Air control	1	103	6.63 ± 0.57	17	6.06	0	89	6.49 ± 0.69	5.24	0
	4	102	10.41 ± 1.27	17	6.00	0.97	89	10.39 ± 1.54	5.24	0
	7	102	15.36 ± 2.18	17	6.00	0.97	89	15.45 ± 2.69	5.24	0
	14	100	29.59 ± 4.19	17	5.88	2.91	89	29.97 ± 5.31	5.24	0
	21	100	45.05 ± 8.16	17	5.88	2.91	89	45.16 ± 9.71	5.24	0
Low dose, 500 mg/m^3	1	90	7.26 ± 0.74	18	5.00	0	102	6.76 ± 0.75	5.66	0
	4	84	11.30 ± 1.15	18	4.67	6.67	95	10.71 ± 1.19	5.28	6.86
	7	84	16.66 ± 1.67	18	4.67	6.67	95	15.64 ± 1.75	5.28	6.86
	14	84	31.39 ± 3.52	18	4.67	6.65	95	29.46 ± 2.72	5.28	6.86
	21	83	50.62 ± 5.34	18	4.61	7.78	94	46.55 ± 5.09	5.22	7.84
High dose, 1,000 mg/m^3	1	135	6.38$^+$ ± 0.62	29	4.66	0	166	6.01$^+$ ± 0.69	5.92	0
	4	92	9.41$^+$ ± 1.48	27	3.41	31.85	101	8.99$^+$ ± 1.59	3.74	39.16
	7	84	13.97$^+$ ± 1.86	25	3.36	37.78	90	13.62$^+$ ± 2.26	3.60	45.78
	14	73	26.46$^+$ ± 5.03	25	2.92	45.93	79	25.93$^+$ ± 5.53	3.16	52.41
	21	47	41.10$^+$ ± 9.52	22	2.14	65.19	44	41.50$^+$ ± 11.15	2.00	73.49

*SD = standard deviation.

+Significant by Students "t" test at p = 0.05.

Table 10. Viability, Survival, and Lactation Indices in a Single Generation During Exposure to White Phosphorus-Felt Smoke for Rat Pups

Index*	Control	Low dose, 500 mg/m^3	High dose, 1,000 mg/m^3
Viability	0.99	0.93	0.64$^+$
21-Day survival	0.98	0.92	0.31$^+$
Lactation	0.99	0.99	0.48$^+$

$$*\text{Viability} = \frac{\text{number of pups alive after 24 hours}}{\text{number of pups born alive}}$$

$$\text{21-Day survival} = \frac{\text{number of pups alive on day 21}}{\text{number of pups alive on day 4}}$$

$$\text{Lactation} = \frac{\text{number of pups alive on day 21}}{\text{number of pups born alive}}$$

$^+$Significant at $p = 0.05$.

4. DISCUSSION

The major teratogenic effects observed in this study included one case each of unilateral anophthalmia and narrow atria in the control-group fetuses; one fetus in the low-dose group had a short tongue and one had narrow atria; brachygnathia was seen in one and narrow atria and thin-walled heart in another fetus in the high-dose group. Ectopic kidneys were observed but are considered to be minor variations. Right ductus arteriosus was observed; but, because this condition was not considered major in a report by Baird, *et al.*,[7] it was considered as minor in this study. Inconsistencies made it difficult to identify WP-felt smoke as the causative factor for the abnormalities since the occurrences were singular and were not supported in the single-generation study; i.e., no pups were born with short tongues or brachygnathia or any other gross abnormalities. Other variations noted were considered minor and would be expected to normalize with continued development of the fetuses (e.g., ectopic testicles and kidneys would descend to the proper areas).

In the dominant lethal mutation study, the successful matings by the males eliminated the possibility that WP-felt smoke inhalation causes male sterility. Significantly more dams mated to males in the low-dose group during the first week following the exposure had at least one resorption site as compared with dams mated to control males. The absence, however, of a significantly higher resorption rate in the high-dose group mating meant there was no dose-related response; i.e., no increase in the number of resorptions per dam in the high-dose mated group over the low-dose and control mated groups.

The single-generation study allows for checks on the teratology and dominant lethal mutation studies. In this study, there were no signs of teratogenic effects. Therefore, it is assumed

that the effects seen in the teratology study were not compound related. Had the increase in the number of dams with resorptions which were mated to males exposed to the low dose been compound related, one would expect to see significantly smaller litters in the single-generation study. This was not so in this study. Though the mean litter size in the single generation was smaller for the low-dose group and smallest for the high-dose group, neither mean was significantly smaller than the controls. It was observed, however, that the mean body weight for the pups in the high-dose group was significantly lower than the mean body weight for the control pups, as were the survivability and viability indices. It cannot be ascertained, however, whether this was a result of: (1) the dams not allowing the young to nurse (the dams often rested some distance from the pups immediately after being returned to the home cage following exposure); (2) the young not being able to nurse because of esophogeal irritation after each exposure; or (3) a combination of the two. Not to be excluded from consideration was the general weakened state of the dams and pups caused by inhaling so much particulate matter. No adverse effects were seen in the low-dose group.

5. SUMMARY

The effect of exposure to airborne white phosphorus smoke at concentrations of 500 and 1,000 mg/m^3 on reproduction in the rat was investigated. Studies conducted included teratology, dominant lethal mutation, and single-generation reproduction.

In the teratogenicity study, one fetus in the high-dose exposure group exhibited brachygnathia and one had narrow atria and a thin-walled heart. One fetus in the low-dose exposure group exhibited a short tongue, and one had narrow atria. One fetus from a control dam exhibited unilateral anophthalmia and one had narrow atria. With only single incidences of the malformations occurring in each group and none in the F_1 offspring from the single-generation study, the variations were noted but not considered to be significant.[3]

In the dominant lethal mutation study, significantly more of the dams which were mated to males exposed to the low dose during the first week following exposure had at least one resorption as compared with dams mated to control males. This was not true for week two dams mated to males from either exposure group. Neither were the mean litter sizes from either exposure group in the single-generation study significantly smaller than that for the control group. So, again, there was no dose relation and no support in the single-generation study for the dominant lethal mutation study findings.

In the single-generation study, the mean body weights were significantly lower for the pups in the high-dose group on each of the five scheduled weighing days. The longer exposure did affect the dams' eating ability as well as that of the pups. The survivability and viability of the pups was significantly decreased below that of the control pups.

It is apparent that, although WP-felt smoke causes no obvious effects on reproductive processes, exposure to high amounts for long periods of time can decrease the quality of life and indeed life expectancy in the rat.

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